REMARKS

This paper is being presented in response to the non-final official action dated January 18, 2007, wherein: (**a**) claims 1-12, 14-17, 39, 40, and 54-67 were pending and examined; (**b**) all of the pending claims were rejected under 35 USC § 112, ¶ 2, as being indefinite; (**c**) claims 39, 40, and 54-67 were rejected under 35 USC § 112, ¶ 1, as reciting subject matter that was not described in the specification; and, (**d**) all of the pending claims were rejected under § 112, ¶ 1, as lacking an enabling disclosure. Reconsideration and withdrawal of the rejections are respectfully requested in view of the foregoing amendments and following remarks.

This paper is timely filed as it is accompanied by a petition under 37 CFR § 1.136(a) for a two-month extension of time to file a response to the outstanding action and authorization for payment of the associated petition fee. Submitted (via first class mail) concurrently with this paper is an information disclosure statement.

The applicants hereby acknowledge with appreciation the courteous interview granted by the examiner on March 21, 2007, to the applicants' representatives (Sandip H. Patel, Keith S. Ruddock, and Malcolm J. Stoker, Ph.D.). The applicants also acknowledge receipt of the examiner's "Interview Summary," at the conclusion of the March 21 interview.

I. Summary of the Claim Amendments

Claims 39, 40, and 54-67 have been canceled without prejudice.

Independent claim 1 has been amended herein and now recites:

> A method of treating chronic pain associated with peripheral neuropathy, the method comprising administering to an individual in need of treatment optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount to treat such chronic pain.

The amended form of the claim adds the phrase "chronic pain associated with," and more clearly, in the manner suggested in the January 18th action, recites the administration amount recited in the prior version of the claim. Written description support for the amendments to independent claim 1, and the phrase "chronic pain associated with," can be found in the specification at, for example, page 18, lines 20-22, page 18, line 30 to page 19, line 1, and page 19, lines 10-11. Therein the specification teaches that the "administration of the inventive composition (e.g., a composition containing an optically pure (S,S) reboxetine) is effective in treating various human conditions including, but not limited to, ... chronic pain, ... peripheral neuropathy ...." At page 10, lines 3-8, 16, and 26, the specification also teaches that the inventive composition can be used to treat "at least one nervous system disorder

selected from the group consisting of ... chronic pain, ... peripheral neuropathy ...." Peripheral neuropathy is art-recognized, diagnosed, and treated as a symptom complex rather than a disease entity. Consequently, the skilled artisan recognizes that treatment of a symptom complex, such as peripheral neuropathy, may be accomplished by alleviating or otherwise controlling one or more symptoms. This treatment is consistent with the teachings in the specification, which state, for example:

> Treatment or prevention of above disorders involves the administration of reboxetine in a manner and form that result in a reduction in the symptoms of the disease or disorder.

Specification at p. 29, lines 12-14. Although the foregoing statement from the specification refers to treatment with (racemic) reboxetine, the skilled artisan, having considered the application's teachings as a whole, would have readily understood that the statement is applicable to treatments with (S,S) reboxetine as well.

Dependent claims 15-17 have been amended herein to more clearly recite that the recited weight percentages are based on the total amount of (S,S) and (R,R) reboxetine present. Written description support for the amendments to these claims can be found in claims 15-17 as originally filed, which recited that the weight percentages were "based on the total weight of the (S,S) and (R,R) reboxetine present." Written description support also can be found in the specification at, for example, page 16, lines 6-7, which defines the term "reboxetine" as referring to a racemic mixture of the (R,R) and (S,S) enantiomers of reboxetine.

No new matter has been introduced by the foregoing claim amendments because the specification provides written description support for the amended claims.

II. The 35 USC § 112, ¶ 2, Rejections Are Mooted by the Claim Amendments

Claims 1-12, 14-17, 39, 40, and 54-67 have been rejected under 35 USC § 112, ¶ 2, as being indefinite. *See* the Action at 12-13. The action states that the independent claims—of which only claim 1 is now pending—are indefinite because each allegedly recites the phrase "therapeutically effective." The action specifically suggests that the rejection relative to the recitation of this phrase in claim 1 can be overcome if the claim is amended to recite "an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount to treat ...." *See* the Action at 12. Accordingly, the applicants have herein amended claim 1 in accordance with that suggestion. The indefiniteness rejection is therefore rendered moot inasmuch as it is premised on the recitation in claim 1 of the offending phrase ("therapeutically effective"). Accordingly, reconsideration and withdrawal of the indefiniteness rejection are respectfully requested.

III. The 35 USC § 112, ¶ 1, "Lack of Written Description" Rejection Is Mooted by the Claim Amendments

Claims 39, 40, and 54-67 have been rejected under 35 USC § 112, ¶ 1, as reciting subject matter allegedly not described in the specification in a manner that reasonably conveys to the ordinarily skilled artisan that the applicants "possessed" the recited subject matter as of the application's filing date. *See* the Action at 9-11. The rejection is moot in view of the cancellation herein of claims 39, 40, and 54-67, without prejudice.

IV. The 35 USC § 112, ¶ 1, "Lack of Enablement" Rejection Is Traversed

Claims 1-12, 14-17, 39, 40, and 54-67 have been rejected under 35 USC § 112, ¶ 1, as allegedly lacking an enabling disclosure. *See* the Action at 3-9. The current action articulates the following basis for the rejection:

> Claims 1-12, 14-17, 39, 40, and 54-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating post-herpetic neuralgia, does not reasonably provide enablement for treating (or preventing) 'peripheral neuropathy'. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.
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> [G]iven the highly unpredictable state of the art and furthermore, given that the applicant does not provide sufficient guidance or direction as to how to make and use the full scope of the presently claimed invention without undue experimentation, the Office would require appropriate disclosure, in the way of scientifically sound reasoning or the way of concrete examples, as to why the data shown is reasonably representative and objective showing such that it was commensurate in scope with and, thus, adequately enables, the use of the elected species for the full scope of the presently claimed subject matter.

See the Action at 3 and 9. This basis was reiterated by the examiner during the March 21 examiner interview. Importantly, during that interview, the examiner provided the applicants' representatives with helpful guidance in addressing the basis for the rejection, and indicated that a response to the rejection should include (a) an amendment to independent claim 1 to recite a "method of treating chronic pain associated with peripheral neuropathy," and (b) a presentation of further scientific evidence demonstrating the efficacy of the claimed method, as amended, in treating chronic pain associated with peripheral neuropathy, in general.

Consistent with the examiner's helpful guidance and indications, the pending claims have been amended herein to recite methods of treating an individual suffering from chronic pain associated with peripheral neuropathy. The methods generally include administration of optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount to treat the chronic pain.

The first action enumerated the various *Wands* factors that the Patent Office considered in determining the applicants' compliance with the § 112, ¶ 1, enablement standard. The applicants addressed each of those *Wands* factors in responding to the first action. The current action, emphasizes only one of the *Wands* factors—the breadth of the claims—in supporting the enablement rejection, and comments on the *Wands* factors relating to the level of ordinary skill in the art, sufficiency of working examples, the state of the prior art, and the predictability in the art. All of these Wands factors are discussed below along with a presentation of scientific evidence consistent with the examiner's helpful guidance and indications.

The rejection is thus traversed, and reconsideration and withdrawal of the rejection are respectfully requested in view of the foregoing claim amendments and the response set forth below.

A. Proper Basis for a § 112, ¶ 1, Lack of Enablement Rejection

For the sake of brevity, the descriptions of the proper basis for a § 112, ¶ 1, lack of enablement rejection, set forth in the responses filed January 17 and August 11, 2006, are incorporated herein by reference.

Claim breadth is merely one of the various *Wands* factors that the Patent Office must consider when determining whether there is sufficient evidence to support a conclusion that a patent application satisfies (or does not satisfy) the enablement requirement, and whether any necessary experimentation is "undue." *See In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The Patent Office, however, may not conclude that a patent application is not enabling based on an analysis of only one of those factors—e.g., the breadth of the claims—while ignoring one or more of the other factors; instead, a conclusion of non-enablement must be based on the evidence as a whole. *See id.* at 740.

A disclosure teaching how to make and use an invention in terms corresponding in scope to the terms defining the claimed subject matter complies with the enablement requirement (in § 112, ¶ 1), *unless* there is a reason to doubt the objective truth of the disclosure relied upon for enabling support. *See In re Marzocchi*, 439 F.2d 220, 223-24 (CCPA 1971). In determining (and reconsidering) whether the patent application includes an enabling disclosure of the claimed invention, the Patent Office must consider *all* evidence in the record, weighing evidence that confirms enablement against evidence that refutes enablement. *See In re Wands*, 858 F.2d at 737, 740.

B. The Non-Enablement Rejection is Traversed

1. The Claimed Invention

The claimed invention relates to methods of treating chronic pain associated with peripheral neuropathy. These methods include administering to an individual in need of treatment optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount to treat such chronic pain.

Claims reciting methods of preventing peripheral neuropathy were canceled from the application in the applicants' amendment filed (January 17, 2006) in response to the first official action. *See e.g.*, canceled claim 38. Consequently, the currently claimed invention does not relate to methods of preventing chronic pain associated with peripheral neuropathy.

2. The Patent Office's Position as Set Forth in the Final Action

Citing various post-filing publications, the action asserts that the term "peripheral neuropathy" is recognized in the art as a term describing a clinical syndrome encompassing a wide range of disorders of the peripheral nervous system. *See* the Action at 4. As explained below, this assertion (whether or not true) does not affect the breadth a skilled artisan would attribute to the claimed invention such that this *Wands* factor—the breadth of the claimed invention—should weigh in favor of a conclusion that the claimed invention lacks an enabling disclosure. The action further asserts that preponderant evidence from the state of the art, as exemplified by the publications cited in the Form PTO-892 accompanying the action, shows that "peripheral neuropathy" encompasses a very broad scope of disorders or disease of the peripheral nervous system characterized by common symptoms of numbness, tingling sensation, a prickling sensation or pain. *See* the Action at 14. The applicants respectfully submit that the publications cited in support of the Patent Office's assertion, as well as the publications cited in the Form PTO-892 that accompanied the action, actually *support the applicants' assertion* that peripheral neuropathy is art-recognized as a disorder of the peripheral nervous system characterized by a complex of common symptoms. These publications also demonstrate that chronic pain is the most prevalent of these common symptoms. *See* Section **IV.B.5**, below.

The applicants respectfully submit that the amended claims, when considered in light of the further scientific evidence presented hereinafter, are enabled according to 35 USC § 112, ¶ 1.

3. Results of *Pre-Clinical* Studies Demonstrate (S,S) Reboxetine's Predicted Efficacy in Treating Painful Peripheral Neuropathy

Appended hereto is a copy of a "Second Declaration of Dr. Malcolm John Stoker Pursuant To 37 CFR §1.132" (hereinafter "the 2007 Stoker declaration"). In the 2007 Stoker declaration, Dr. Stoker recounts certain aspects of his prior "Declaration of Dr. Malcolm John

Stoker Pursuant to 37 CFR § 1.132," dated July 31, 2006 (hereinafter "the 2006 Stoker declaration").

The 2006 Stoker declaration represented that peripheral neuropathy "is art-recognized and diagnosed as a 'symptom complex' rather than a disease entity," and treatment of a symptom complex may be accomplished by alleviating or otherwise controlling one or more symptoms. Pain is a known major symptom of peripheral neuropathy requiring treatment (*see* the 2007 Stoker declaration at ¶ 7), and the claims, as amended herein recite methods of treating an individual suffering from chronic pain associated with peripheral neuropathy. The 2006 Stoker declaration also represented that diabetic peripheral neuropathy (DPN) and post herpetic neuralgia (PHN) are major types of peripheral neuropathy characterized by the representative neuropathic pain symptoms requiring treatment. *See* the 2007 Stoker declaration at ¶ 8.

The 2006 Stoker declaration additionally represented that Pfizer Study Protocol A6061001 demonstrated in a Phase II clinical trial that (S,S) reboxetine provided effective relief to patients suffering from chronic pain associated with PHN that had failed to respond to gabapentin treatment. *See* the 2007 Stoker declaration at ¶ 9. The 2006 Stoker declaration stated that, because PHN is a representative disorder to study when considering the effective treatment of painful peripheral neuropathy, it is reasonable to conclude that (S,S) reboxetine would be effective in the general treatment of painful peripheral neuropathy. *See* the 2007 Stoker declaration at ¶ 10. That conclusion is further supported by further representations set forth in the 2007 Stoker Declaration and described below.

As a result of the finding in the instant application that (S,S) reboxetine is a highly selective norepinephrine reuptake inhibitor and may be useful for the treatment of chronic pain associated with peripheral neuropathy, a neuroanatomical rationale for the efficacy of (S,S) reboxetine in the treatment of painful peripheral neuropathy in general can now be provided as follows.

(a) Norepinephrine transporters (NETs) provide the primary mechanism whereby the action of norepinephrine at the noradrenergic synapse is terminated.

(b) Consequently, inhibitors of NET lead to enhanced noradrenergic transmission.

(c) Investigations using neuronal lesions in the periphery and brain support a localization of NETs to innervating, noradrenergic terminals rather than target cells.

(d) An inhibitory, descending noradrenergic pathway, from the nuclei of the brainstem and mid-brain that terminates on neurons of the dorsal horn, is thought to play a role in pain transmission.

(e) Enhancing descending noradrenergic transmission to the spinal cord would be expected to decrease the transmission of painful stimuli to the brain through inhibitory actions at the superficial laminae of the dorsal horn of the spinal cord.

(f) Selective norepinephrine reuptake inhibition by (S,S) reboxetine is thus expected to provide effective pain relief for the treatment of chronic pain associated with peripheral neuropathy, such as painful neuropathy in patients with diabetes mellitus, post herpetic neuralgia, and chronic pain associated with other forms of peripheral neuropathy.

See the 2007 Stoker declaration at ¶ 11.

This expectation is further supported by the results obtained from pre-clinical, *in vivo*, proof-of-concept experiments, which were performed with (S,S) reboxetine to treat neuropathic pain in three well-established animal models: (a) the Chung (rat) model; (b) the Bennett (rat) model; and, (c) the diabetic streptozocin mouse model. The first two of these pre-clinical animal models (i.e., models (a) and (b)) involve the induction of traumatic nerve injury and are widely used to screen potential drugs for efficacy in treating pain associated with peripheral neuropathies of diverse origin. The last of these pre-clinical animal models (i.e., model (c)) involves the induction of diabetes in mice via administration of streptozocin, and is predictive for the efficacy of treating pain in patients with diabetic peripheral neuropathy (DPN). *See* the 2007 Stoker declaration at ¶s 12-15.

The results obtained in these models of neuropathic pain are summarized in the Table appended as Appendix 1 to the 2007 Stoker declaration. These results support the rationale that (S,S) reboxetine may be used for the treatment of painful peripheral neuropathy in general, and leads to the prediction that (S,S) reboxetine will be useful to treat an individual suffering from chronic pain associated with peripheral neuropathy. More specifically, the IP dose-response study in the rat chronic constriction injury ("CCI") model compared (S,S) reboxetine with amitriptyline and gabapentin—drugs known to be effective in experimental studies of chronic pain associated with peripheral neuropathy. (S,S) reboxetine and gabapentin were effective in this model (and amitriptyline induced variable results). In a further study in this rat CCI model, (S,S) reboxetine induced reversal of tactile allodynia as did gabapentin and nortriptyline—drugs known to be effective in experimental studies of chronic pain associated with peripheral neuropathy— further indicating efficacy of (S,S) reboxetine in this peripheral neuropathy model. In the study in the rat sciatic nerve ligation ("SNL") model, subcutaneous (SC) administration of (S,S) reboxetine was shown to have efficacy that was

dose—and time—dependent. That study also shows that (S,S) reboxetine is the more active enantiomer in this painful peripheral neuropathy model. In another study, performed in mice having diabetic peripheral neuropathy, (S,S) reboxetine demonstrated efficacy in relieving thermal hyperalgesia as did gabapentin and amitriptyline. *See* the 2007 Stoker declaration at ¶ 16.

4. Results of Additional *Clinical* Studies Demonstrate (S,S) Reboxetine's Efficacy in Treating Painful Peripheral Neuropathy

Pfizer has initiated additional clinical studies for (S,S) reboxetine since completing Pfizer Study Protocol A6061001. Specifically, Pfizer has initiated a long-term, open label study (Pfizer Study Protocol A6061031) in patients with painful diabetic peripheral neuropathy (DPN). *See* ClinicalTrials.gov Identifier: NCT00348894, available at http://clinicaltrials.gov/ct/show/NCT00348894?order=4 (version last updated June 4, 2007) ("The purpose of this study is to assess the long-term safety and tolerability of [S,S]-Reboxetine in patients with chronic painful diabetic peripheral neuropathy.") (copy appended as Appendix 2 to the 2007 Stoker declaration. At the assessment point of April 1, 2007, 36 patients had been treated with (S,S) reboxetine in this study. An interim evaluation of the efficacy data from this study indicates an evolving pain response with time with those patients on (S,S) reboxetine. This is illustrated in the Figure appended as Appendix 3 to the 2007 Stoker declaration.* This interim study result indicates that (S,S) reboxetine is efficacious in the treatment of painful DPN. *See* the 2007 Stoker Declaration at ¶ 18. This interim evaluation in this on-going clinical study (Pfizer Study Protocol A6061031), coupled with the results of the aforementioned Pfizer Study Protocol A6061001, support the efficacy of (S,S) reboxetine in treating chronic pain arising from two representative peripheral neuropathies, i.e., DPN and PHN. *See* the 2007 Stoker Declaration at ¶ 19.

Given the efficacy demonstrated by (S,S) reboxetine in a range of *pre-clinical* studies predictive of efficacy in the treatment of painful peripheral neuropathy, and the efficacy shown in completed or on-going *clinical* studies involving patients suffering from chronic pain

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* "STCA" in the Figure refers to "Standard Care":

> Patients randomized to standard care will receive treatment optimized for them on an individual basis. The investigator will be free to provide whatever pharmacological (other than reboxetine/Edronax or opioids) or other treatment considered optimal for management of the patient's pain, taking into consideration any side effects associated with this individualized therapy. This treatment arm is intended to reflect current routine best medical practice in the management of neuropathic pain. It thus provides a comparative context for the interpretation of the safety and tolerability data obtained for [S,S]-RBX [(S,S) reboxetine].

associated with PHN and DPN, it is reasonable to conclude that (S,S) reboxetine would be effective to treat an individual suffering from chronic pain associated with peripheral neuropathy.

5. Publications Cited by the Patent Office Support the Applicants' Interpretation of Peripheral Neuropathy

The action asserts that preponderant evidence from the state of the art, as exemplified by the publications cited in the Form PTO-892 accompanying the action, shows that "peripheral neuropathy" encompasses a very broad scope of disorders or disease of the peripheral nervous system characterized by common symptoms of numbness, tingling sensation, a prickling sensation or pain. *See* the Action at 14. The applicants respectfully submit that the publications cited in support of the Patent Office's assertion, as well as the publications cited in the Form PTO-892 that accompanied the action, actually *support the applicants' assertion* that peripheral neuropathy is art-recognized as a disorder of the peripheral nervous system characterized by a complex of common symptoms, and that methods of treating peripheral neuropathy actually treat one or more of the symptoms—rather than the underlying cause. These publications also demonstrate that chronic pain is the most prevalent of these common symptoms. The applicants' representatives discussed many of these publications with the examiner during the March 21 examiner interview. The examiner appeared to be persuaded by the applicants' position. Accordingly, the discussion below is presented simply to create a record response to the Patent Office position set forth in the action.

(a) England *et al.* (**2004**) *The Lancet* **363**:2151-61.

England et al. teach that the term "peripheral neuropathy" is a "general term that indicates any disorder of the peripheral nervous system." *See* England *et al.*, at 2151. England et al. also teach that treatment of pain is an important aspect in treating peripheral neuropathy:

> Treatment of peripheral neuropathy is divided into those that are specific for the subtype of neuropathy, and those that are useful for neuropathies in general. ... *Symptomatic management is important for all types of neuropathy*, including general preventive and palliative therapy *as well as the treatment of specific problems such as neuropathic pain.*
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> Treatment of pain is an important aspect for many patients with chronic polyneuropathies.

Id. at 2159 (emphases added).

(b) Robert W. Shields, Jr., "*Peripheral Neuropathy*", published February 9, 2004, www.clevelandclinicmeded.com (15 pages).

Shields teaches that the term "peripheral neuropathy" refers to clinical syndromes and that pain peripheral neuropathies present with pain:

> Peripheral neuropathy, in the broadest sense, refers to a scope of clinical syndromes affecting a variety of peripheral nerve cells and fibers. Most peripheral neuropathies affect all fiber types to some extent. However, a single fiber type may be predominantly or exclusively affected in some disorders. For example, in small-fiber neuropathy (SFN), small-caliber, unmyelinated, or only thinly myelinated autonomic fibers and somatic sensory fibers that subserve pain and thermal receptors are predominantly involved. Thus, patients with SFN present primarily with pain and autonomic dysfunction.

Shields at 2. Shields also teaches that pain is predominant among the symptoms associated with peripheral neuropathies:

> A host of symptoms and signs that reflect sensory, motor, and autonomic nerve fiber dysfunction are typical of peripheral neuropathies, and *some combinations of symptoms and signs may be recognized as specific syndromes of peripheral nerve disease. ... Typically, all sensory modalities are affected to some extent, including ... pain.*
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> In certain polyneuropathies, pain predominates in the clinical picture and the sensory examination tends to disclose deficits predominantly of pain .... *Pain is a serious symptom for many patients* ....
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Id. at 4-5 (emphases added). Shields further teaches that patients suffering from painful polyneuropathies have been known to respond to drugs administered to manage the pain.

> In those patients who have associated pain, particularly patients with SFN, specific neuropathic pain management is instituted. *Neuropathic pain typically does not respond to simple analgesics, and its potential chronicity precludes narcotic therapy as a first choice*. Typically, patients with SFN and other painful polyneuropathies respond to drugs known to be effective for neuropathic pain, including tricyclic antidepressants and a variety of antiepileptic drugs and membrane stabilizers.

Id. at 12 (emphasis added). Shields also teaches that the symptoms of polyneuropathy can be treated with medications for neuropathic pain:

> In most patients with a peripheral neuropathy related to a medical disorder or immune-mediated mechanism, specific therapies directed at the underlying mechanism are usually effective in controlling the peripheral neuropathy. *However, despite these therapies, the symptoms and signs of the peripheral neuropathy remain a chronic problem in most patients. Nevertheless,* even in the absence of a specific treatable etiology, *the symptoms of polyneuropathy can be treated with* a variety of supportive measures including *medications for neuropathic pain*, physical therapy modalities, and orthodic devices.

Id. at 13 (emphases added).

(c) Barrett, "*Peripheral Neuropathy*," Gale Encyclopedia of Medicine, 1999 (9 pages).

Barrett teaches a number of peripheral neuropathies commonly presenting with a pain symptom:

> Typical symptoms of neuropathy are related to the type of affected nerve. *If a sensory nerve is damaged, common symptoms include ... pain*. Pain associated with neuropathy can be quite intense and may be described as cutting, stabbing, crushing, or burning. In some cases, a non-painful stimulus may be perceived as excruciating or pain may be felt even in the absence of a stimulus.
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> The diabetes-peripheral neuropathy link has been well established. A typical pattern of diabetes-associated neuropathic symptoms includes sensory effects that first begin in the feet. The associated pain or pins-and-needles ... sensations form a typical "stocking" distribution in the feet and lower legs.
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> Infection with certain viruses is associated with extremely painful sensory neuropathies.

Barrett at 3-4 (emphasis added). Barrett also teaches that an immediate symptom of a physical injury affecting one nerve or a group of closely associated nerves is pain. *Id.* at 4. Barrett further teaches that pain also is a common symptom of neuropathy caused by drugs, alcohol, exposure to heavy metals, or malnutrition by thiamine (vitamin B_1) deficiency:

> Neuropathy that is caused by drugs usually involves sensory nerves on both sides of the body, particularly in the hands and feet, and *pain is a common symptom.* ... [Exposure to] thallium produces painful sensorimotor neuropathy.
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> Burning, stabbing pains and numbness in the feet, and sometimes in the hands, are distinguishing features of alcoholic neuropathy.
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> [T]hiamine (vitamin B_1) deficiency is the cause of beriberi, a neuropathic disease characterized by heart failure and painful polyneuropathy of sensory nerves.

Id. at 5 (emphasis added). Barrett further teaches that the treatment of peripheral neuropathy may focus on pain management:

> *Treatment may focus more on symptom management than on combating the underlying cause*, at least until a definitive diagnosis has been made. ... *Because pain is associated with many of the neuropathies, a pain management plan may need to be mapped out, especially if the pain becomes chronic*.

Id. at 6 (emphases added).

(d) "NINDS Peripheral Neuropathy Fact Sheet", 2006, www.ninds.nih.gov (8 pages), and "NINDS Peripheral Neuropathy Information Page," 2006, www.ninds.nih.com (3 pages).

The National Institute of Neurological Disorders ("NINDS"), a component of the Federal government's National Institutes of Health, has primary responsibility for research on peripheral neuropathy and sponsored research aimed at developing effective therapies directed to the pain symptom of peripheral neuropathy:

> *Neuropathic pain is a primary target of NINDS-sponsored studies aimed at developing more effective therapies for symptoms of peripheral neuropathy.* Some scientists hope to identify substances that will block the brain chemicals that generate pain signals, while others are investigating the pathways by which pain signals reach the brain.

See the Fact Sheet at 6 (emphasis added); *see also* the Information Sheet at 1 (emphasis added). The NINDS publications teach that pain is a common symptom in patients suffering from common forms of polyneuropathy. *See* the Fact Sheet at 1-4; *see also* the Information Sheet at 1.

(e) "Peripheral Neuropathy," November 1, 2005, MayoClinic.com (2 pages).

This Mayo Clinic publication teaches that "treatment of peripheral neuropathy may focus on managing pain." Mayo Clinic publication at 1.

(f) Chang, "*Diagnosis of Peripheral Neuropathies*," CNI Review, Vol. 13, No. 2 (2002) (9 pages).

Chang teaches that typical symptoms of peripheral neuropathy include pain:

> Typical symptoms of peripheral neuropathy are numbness and tingling in the feet and hands that may progress proximally with varying degrees of muscle weakness, atrophy, ataxia, painful paresthesias, and autonomic dysfunction.

Chang at 1. Chang further teaches that treatment of peripheral neuropathies "is usually symptomatic." *Id.* at 8

(g) Rowett, "Diabetic Neuropathy, " www.health.yahoo.com (2004) (3 pages).

Rowett teaches that diabetic neuropathy is "a nerve disorder commonly caused by diabetes," and that injury to the nerves may limit an individual's "ability to feel pain." Rowett at 1. Rowett further teaches that "[t]reatment will be tailored to your symptoms," and that medications can be used "to relieve pain associated with peripheral neuropathy." *Id.* at 2.

(h) Chambliss, "Question and Answer," ARCH FAM MED, Vol. 7, pp. 470-71 (Sept/Oct 1998).

In this Q/A discourse, Chambliss discusses the use of fluoxetine to treat pain associated with diabetic sensory neuropathy, demonstrating that the art's attempts to treat the pain symptom associated with peripheral neuropathy:

> A few studies have examined whether SSRIs are valuable in relieving the pain of diabetic neuropathy. ... The end points evaluated were daily pain scores and global pain relief at the end of treatment [with the SSRIs].

Chambliss at 470.

(i) Sternberg, "*Diabetic Peripheral Neuropathy: Current Concepts and Treatment*," Northeast Florida Medicine, 23-26 (www.DCMS online.org) (2005).

Sternberg teaches that diabetic peripheral neuropathy is a significant cause of pain in patients with diabetes mellitus and that diabetic peripheral neuropathy is a type of neuropathic pain (i.e., pain caused by damage or dysfunction of the nervous system). Sternberg at 23. Sternberg further teaches medications known to treat diabetic peripheral neuropathy do not relieve the pain completely and that a moderate degree of pain relief is a practical goal of treatment. *Id.*

(j) Santillan, "*Management of Diabetic Peripheral Neuropathic Pain*," Business Briefing: North American Pharmacotherapy, 53-54 (2005).

Santillan generally teaches that therapeutic agents, such as tricyclic drugs, are useful for the management of pain in patients suffering from diabetic peripheral neuropathy. Santillan at 54.

(k) Shlay *et al.* (**1998**) *JAMA* **280**:1590-95.

Shlay et al. further acknowledge the art's recognition of treating the pain associated with HIV-related peripheral neuropathy, specifically examining the efficacy of amitriptyline in mediating the pain. Shlay at 1590. Shlay et al. conclude that amitriptyline was not effective; however, they also recognize that the treatment of peripheral neuropathy includes the management of the pain symptom associated with peripheral neuropathy. *Id.* at 1595.

6. The Ordinary Skill in the Art, Sufficiency of Working Examples, the State of the Prior Art, and the Predictability an the Art

The action states that the "relative skill of those in the art of pharmaceuticals and the unpredictability in the pharmaceutical art is very high," and concludes that the "physiological or pharmaceutical activity of treating (or preventing) peripheral neuropathy prior to filing of the instant invention was an unpredictable art." Action at 6-7.

The Patent Office previously alleged that the level of skill in the art is generally that of "a Ph.D. or M.D. with expertise in the area of neurology." *See* Official Action, dated October 19, 2005, at 4. The applicants did not dispute that allegation, but submitted that an example of a Ph.D. with expertise in the area of neurology is a person having a Ph.D. in pharmacology and experience in the neurosciences. *See* "Amendment 'A' and Response to Official Action," dated January 11, 2006, at 13 and 23-24. As argued in the applicants' prior communications to the Patent Office, a person having a Ph.D. in pharmacology and experience in the neurosciences would readily recognize in the prior art's teachings that gabapentin can be used to manage pain-related responses in several models of neuropathic pain. Gabapentin is commercially-available as Neurontin®, which is manufactured by Pfizer Inc. (the successor-in-interest to the assignee of the current application), and has been FDA-approved for the treatment of postherpetic neuralgia in adults. As previously noted, the Rosner et al. article (Rosner et al. (**1996**) *Clin. J. Pain* **12**:56-58) describes the successful use of gabapentin to treat painful peripheral neuropathy, including post-herpetic neuralgia, and provides dosing information. Indeed the published product insert for Neurontin® includes a description of how to administer Neurontin® to treat the approved indications (including post-herpetic neuralgia). Thus, the art recognized suitable formulations (gabapentin) and dosing regimens to actively treat painful peripheral neuropathy.

The application provides ample direction to a person having a Ph.D. in pharmacology and experience in the neurosciences such that the person could prepare a suitable pharmaceutical composition containing (S,S) reboxetine and determine a suitable dosing regimen to treat an individual suffering from chronic pain associated with peripheral neuropathy. Specifically, the specification describes *how to make* the composition recited in the claimed treatment methods at, for example, page 22, line 1, to page 24, line 11. The specification describes *how to practice* the claimed methods by specifying desirable and preferable daily doses at, for example, page 24, line 12, to page 25, line 3. The specification further states, at page 25, line 29, to page 26, line 2, that "the optimum daily dosage for each patient must be determined by a treating physician taking into account each patient's size, other medications which the patient is taking, identity and severity of the disorder, and all of the other circumstances of the patient." The Patent Office has not articulated any disagreement with the foregoing facts.

The action states that the art generally recognized that not all antidepressants would work similarly in the treatment of various types of peripheral neuropathy, citing to an instance where fluoxetine was ineffective in treating diabetic neuropathy. The applicants have found that (S,S) reboxetine is a highly selective noradrenaline (norepinephrine) reuptake inhibitor devoid of effects on other neurotransmitters (*see* the 2006 Stoker declaration at ¶ 18), in contrast to fluoxetine, which is a selective serotonin reuptake inhibitor. The Rule 132

declarations of record demonstrate that administration of (S,S) reboxetine is effective in well-established models predictive of a compound's efficacy in treating pain associated with peripheral neuropathy. Consequently, there remains no relevant unpredictability with respect to the claimed subject matter.

The current action states that the application sets forth "only a limited number of example[s]" that "are neither exhaustive, nor define the class of diseases required." The applicants resubmit that compliance with the enablement requirement *does not* turn on whether the patent application discloses a working example. MPEP § 2164.02 (8th ed. Rev. 5, Aug. 2006). Notwithstanding, the Rule 132 declarations now of record, including the 2007 Stoker declaration discussed herein, report pre-clinical and clinical data demonstrating the efficacy of (S,S) reboxetine in well-established models used to screen potential drugs for efficacy in treating pain associated with peripheral neuropathies of diverse origin, and in patients suffering from representative painful peripheral neuropathies. Those declarations and the data reported therein support the applicants' position that (S,S) reboxetine would be effective to treat chronic pain associated with peripheral neuropathy, in accordance with the claimed methods. "[B]ecause only an enabling disclosure is required, applicant[s] need not describe *all* actual embodiments." *Id.* (emphasis added).

In view of the foregoing, the applicants respectfully (re)submit that consideration of the *Wands* factors relating to the level of ordinary skill in the art, sufficiency of working examples, the state of the prior art, and the predictability in the art *all* weigh in favor of a conclusion that a person having a Ph.D. in pharmacology and experience in the neurosciences cognizant of the prior art (and predictability in the prior art) would have had no reason to doubt whether the claimed method of treating an individual suffering from chronic pain associated with peripheral neuropathy would work. The applicants further submit that the Rule 132 declarations of record present concrete examples and scientifically sound reasoning demonstrating that the data obtained from those examples are a reasonably representative and objective showing commensurate in scope with, and, thus, adequately enable the use of (S,S) reboxetine for, the full scope of the presently claimed subject matter.

In reconsidering whether the patent application includes an enabling disclosure of the claimed invention, the Patent Office must consider all evidence in the record (including the patent application), weighing evidence that confirms enablement against evidence that refutes enablement. *See In re Wands*, 858 F.2d at 737, 740. Accordingly, the reconsideration and withdrawal of the § 112, ¶ 1, enablement rejection are respectfully requested.

CONCLUSION

In view of the foregoing, cancellation of claims 39, 40, and 54-67, entry of the amendments to claims 1 and 15-17, consideration of the appended declaration, reconsideration and withdrawal of the rejections, and allowance of all pending claims 1-12 and 14-17 are respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form or procedure in an effort to advance this application to allowance, the examiner is urged to contact the undersigned attorney.

Respectfully submitted,

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June 18, 2007

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